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(54) Title: N-LINKED UREAS AND CARBAMATES OF HETEROCYCLIC THIOESTERS

(57) Abstract

This invention relates to neurotrophic low molecular weight, small molecule N-linked ureas and carbamates of heterocyclic thioesters having an affinity for FKBP-type immunophilins, and their use as inhibitors of the enzyme activity associated with immunophilin proteins, particularly peptidyl-prolyl isomerase, or rotamase, enzyme activity.

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N-LINKED UREAS AND CARBAMATES OF HETEROCYCLIC THIOESTERS

This application is a continuation-in-part application of U.S. Patent Application Serial No. 08/775,585 filed December 31, 1996.

BACKGROUND OF THE INVENTION

1. Field of Invention

This invention relates to neurotrophic low molecular weight, small molecule N-linked ureas and carbamates of heterocyclic thioesters having an affinity for FKBP-type immunophilins, and their use as inhibitors of the enzyme activity associated with immunophilin proteins, particularly peptidyl-prolyl isomerase, or rotamase, enzyme activity.

2. Description of Related Art

The term immunophilin refers to a number of proteins that serve as receptors for the principal immunosuppressant drugs, cyclosporin A (CsA), FK506 and rapamycin. Known classes of immunophilins are cyclophilins and FK506 binding proteins, or FKBPs. Cyclosporin A binds to cyclophilin A while FK506 and rapamycin bind to FKBP12. These immunophilin-drug complexes interface with various intracellular signal transduction systems, especially the immune and nervous systems.

Immunophilins are known to have peptidyl-prolyl

isomerase (PPIase), or rotamase, enzyme activity. It has been determined that rotamase enzyme activity plays a role in the catalyzation of the interconversion of the cis and trans isomers of peptide and protein substrates for the immunophilin proteins.

Immunophilins were originally discovered and studied in the immune tissue. It was initially postulated by those skilled in the art that inhibition of the immunophilins' rotamase activity leads to inhibition of T-cell proliferation, thereby causing the immunosuppressive activity exhibited by immunosuppressant drugs, such as cyclosporin A, FK506 and rapamycin. Further study has shown that the inhibition of rotamase activity, in and of itself, does not result in immunosuppressive activity. Schreiber et al., *Science*, 1990, vol. 250, pp. 556-559. Instead, immunosuppression appears to stem from the formulation of a complex of immunosuppressant drugs and immunophilins. It has been shown that the immunophilin-drug complexes interact with ternary protein targets as their mode of action. Schreiber et al., *Cell*, 1991, vol. 66, pp. 807-815. In the case of FKBP-FK506 and cyclophilin-CsA, the immunophilin-drug complexes bind to the enzyme calcineurin and inhibit the T-cell receptor signalling which leads to T-cell

proliferation. Similarly, the immunophilin-drug complex of FKBP-rapamycin interacts with the RAFT1/FRAP protein and inhibits the IL-2 receptor signalling.

Immunophilins have been found to be present at high concentrations in the central nervous system. Immunophilins are enriched 10-50 times more in the central nervous system than in the immune system. Within neural tissues, immunophilins appear to influence nitric oxide synthesis, neurotransmitter release and neuronal process extension.

It has been found that picomolar concentrations of an immunosuppressant such as FK506 and rapamycin stimulate neurite outgrowth in PC12 cells and sensory neurons, namely dorsal root ganglion cells (DRGs). Lyons et al., *Proc. of Natl. Acad. Sci.*, 1994, vol. 91, pp. 3191-3195. In whole animal experiments, FK506 has been shown to stimulate nerve regeneration following facial nerve injury.

Surprisingly, it has been found that certain compounds with a high affinity for FKBPs are potent rotamase inhibitors and exhibit excellent neurotrophic effects. Furthermore, these rotamase inhibitors are devoid of immunosuppressive activity. These findings suggest the use of rotamase inhibitors in treating various peripheral neuropathies and enhancing neuronal

regrowth in the central nervous system (CNS). Studies have demonstrated that neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) may occur due to the loss, or decreased availability, of a neurotrophic substance specific for a particular population of neurons affected in the disorder.

Several neurotrophic factors affecting specific neuronal populations in the central nervous system have been identified. For example, it has been hypothesized that Alzheimer's disease results from a decrease or loss of nerve growth factor (NGF). It has thus been proposed to treat Senile Dementia of the Alzheimer's Type (SDAT) patients with exogenous nerve growth factor or other neurotrophic proteins, such as brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor and neurotropin-3, to increase the survival of degenerating neuronal populations.

Clinical application of these proteins in various neurological disease states is hampered by difficulties in the delivery and bioavailability of large proteins to nervous system targets. By contrast, immunosuppressant drugs with neurotrophic activity are relatively small and display excellent bioavailability and specificity. However, when

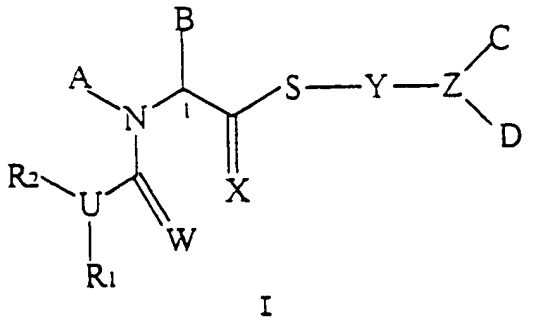
administered chronically, immunosuppressant drugs exhibit a number of potentially serious side effects including nephrotoxicity, such as impairment of glomerular filtration and irreversible interstitial fibrosis (Kopp et al., *J. Am. Soc. Nephrol.*, 1991, 1:162); neurological deficits, such as involuntary tremors, or non-specific cerebral angina, such as non-localized headaches (De Groen et al., *N. Engl. J. Med.*, 1987, 317:861); and vascular hypertension with complications resulting therefrom (Kahan et al., *N. Engl. J. Med.*, 1989, 321:1725).

In order to prevent the side effects associated with use of the immunosuppressant compounds, the present invention provides non-immunosuppressive compounds containing small molecule FKBP rotamase inhibitors for enhancing neurite outgrowth, and promoting neuronal growth and regeneration in various neuropathological situations where neuronal repair can be facilitated, including: peripheral nerve damage caused by physical injury or disease state such as diabetes; physical damage to the central nervous system (spinal cord and brain); brain damage associated with stroke; and neurological disorders relating to neurodegeneration, such as Parkinson's disease, SDAT (Alzheimer's disease), and amyotrophic lateral sclerosis.

SUMMARY OF THE INVENTION

The present invention relates to neurotrophic, low molecular weight, small molecule compounds having an affinity for FKBP-type immunophilins. Once bound to these proteins, the neurotrophic compounds are potent inhibitors of the enzyme activity associated with immunophilin proteins, particularly peptidyl-prolyl isomerase, or rotamase, enzyme activity. A key feature of the compounds of the present invention is that they do not exert any significant immunosuppressive activity in addition to their neurotrophic activity. Another significant feature is the novel addition of a thioester linkage and an unexpected increase in bioavailability and potency as compared to compounds lacking a thioester linkage.

Specifically, the present invention relates to a compound of formula I:



I

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A and B are taken together with the nitrogen and carbon atoms to which they are respectively attached

to form a 5-7 membered saturated or unsaturated heterocyclic ring containing any combination of CH_2, O, S, SO, SO_2, NH or NR_1;

X is either O or S;

Y is a direct bond to Z, a C_1-C_3 straight or branched chain alkyl, or a C_2-C_3 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_1, S, SO, or SO_2, wherein R_1 is selected from the group consisting of hydrogen, (C_1-C_3)-straight or branched chain alkyl, (C_3-C_8)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

Z is a direct bond, or a C_1-C_3 straight or branched chain alkyl, or a C_2-C_3 straight or branched

chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_3)-straight or branched chain alkyl, (C_3-C_4)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_2 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

C and D are independently:

hydrogen, Ar, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more position(s) with C_3-C_6 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl groups are optionally substituted with C_1-C_3 alkyl, C_2-C_3 alkenyl,

hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_4)-straight or branched chain alkyl, (C_2-C_4)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_2 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

wherein Ar is an aryl or heteroaryl moiety which is substituted or unsubstituted;

W is oxygen or sulfur;

U is either O or N, wherein when U is O, then R_1 is a lone pair of electrons and R_2 is selected from the group consisting of:

Ar as defined above, C_3-C_8 cycloalkyl, C_1-C_8 straight or branched chain alkyl or alkenyl, or C_1-C_8 straight or branched chain alkyl or alkenyl substituted in one or more positions with Ar, amino,

halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_5 straight or branched chain alkyl, C_2-C_5 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2, O, or NR_1 wherein R_1 is selected from the group consisting of hydrogen, (C_1-C_3)-straight or branched chain alkyl, (C_3-C_5)-straight or branched chain alkenyl or alkynyl, and (C_1-C_3) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_6 cycloalkyl;

and when U is N, R_1 and R_2 are selected independently from the group consisting of:

hydrogen, Ar as defined above, C_3-C_6 cycloalkyl, C_1-C_5 straight or branched chain alkyl or alkenyl, or C_1-C_5 straight or branched chain alkyl or alkenyl substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_5 straight or branched chain alkyl, C_2-C_5 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino,

alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2, O, or NR_1 wherein R_1 is selected from the group consisting of hydrogen, (C_1-C_3)-straight or branched chain alkyl, (C_3-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_6 cycloalkyl;

or R_1 and R_2 may be taken together to form a heterocyclic ring.

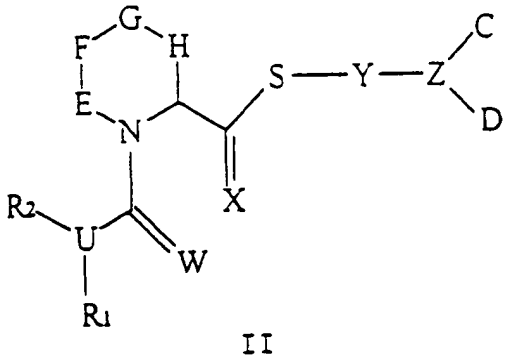
In preferred embodiments, Ar is a cyclic or fused cyclic ring and includes a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted in one to five position(s) with halo, haloalkyl, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_6 alkoxy, C_2-C_6 alkenyloxy, phenoxy, benzyloxy, amino, thiocarbonyl, ester, thioester, cyano, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl; wherein the individual ring sizes are 3-8 members; wherein the heterocyclic ring contains 1-4

heteroatom(s) selected from the group consisting of O, N, or S; wherein aromatic or tertiary alkyl amines are optionally oxidized to a corresponding N-oxide.

Particularly preferred Ar groups include phenyl, benzyl, naphthyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

Preferred heterocyclic groups may be selected from the group consisting of pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, thienyl, piperidinyl, and piperazinyl.

A preferred embodiment of this invention is a compound of formula II:



II

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

E, F, G and H are independently CH_2, O, S, SO, SO_2, NH or NR_1 wherein at least two of E, F, G, and H

are CH_2;

X is either O or S;

Y is a direct bond to Z, a C_1-C_6 straight or branched chain alkyl, or a C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_1-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

Z is a direct bond, or a C_1-C_6 straight or branched chain alkyl, or a C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl,

thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_1, S, SO, or SO_2, wherein R_1 is selected from the group consisting of hydrogen, (C_1-C_4)-straight or branched chain alkyl, (C_1-C_4 -straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

C and D are independently:

hydrogen, Ar, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more position(s) with C_3-C_8 cycloalkyl, C_5-C- cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl groups are optionally substituted with C_1-C_6 alkyl, C_2-C_6 alkenyl, hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl,

sulfonyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_1, S, SO, or SO_2, wherein R_1 is selected from the group consisting of hydrogen, (C_1-C_8)-straight or branched chain alkyl, (C_2-C_8)-straight or branched chain alkenyl or alkynyl, and (C_1-C_3) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

wherein Ar is an aryl or heteroaryl moiety which is substituted or unsubstituted;

W is oxygen or sulfur;

U is either O or N, wherein when U is O, then R_2 is a lone pair of electrons and R_2 is selected from the group consisting of:

Ar as defined above, C_3-C_7 cycloalkyl, C_1-C_8 straight or branched chain alkyl or alkenyl, or C_1-C_8 straight or branched chain alkyl or alkenyl substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_8 straight or branched chain alkyl, C_2-C_8 straight or branched chain alkenyl, carboxyl, thiocarbonyl, ester,

thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2, O, or NR_3 wherein R_3 is selected from the group consisting of hydrogen, (C_1-C_3)-straight or branched chain alkyl, (C_1-C_3)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_3 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_6 cycloalkyl;

and when U is N, R_1 and R_2 are selected independently from the group consisting of:

hydrogen, Ar as defined above, C_3-C_6 cycloalkyl, C_1-C_6 straight or branched chain alkyl or alkenyl, or C_1-C_6 straight or branched chain alkyl or alkenyl substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are

optionally replaced with S, SO, SO_2, O, or NR_3 wherein R_3 is selected from the group consisting of hydrogen, (C_1-C_3)-straight or branched chain alkyl, (C_1-C_4)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_3 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_8 cycloalkyl;

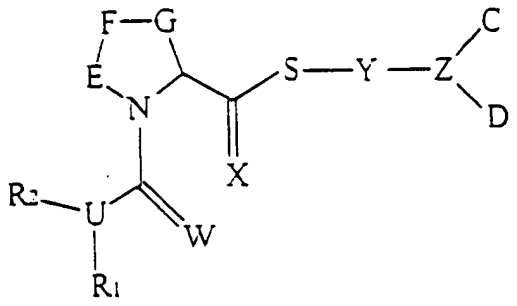
or R_1 and R_2 may be taken together to form a heterocyclic ring.

In preferred embodiments, Ar is a cyclic or fused cyclic ring and includes a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted in one to five position(s) with halo, haloalkyl, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_6 alkoxy, C_2-C_6 alkenyloxy, phenoxy, benzyloxy, amino, thiocarbonyl, ester, thioester, cyano, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl; wherein the individual ring sizes are 5-8 members; wherein the heterocyclic ring contains 1-4 heteroatom(s) selected from the group consisting of O, N, or S; wherein aromatic or tertiary alkyl amines are optionally oxidized to a corresponding N-oxide.

Particularly preferred Ar groups include phenyl, benzyl, naphthyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

Preferred heterocyclic groups may be selected from the group consisting of pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, thienyl, piperidinyl, and piperazinyl.

Another preferred embodiment is a compound of formula III:



III

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

E, F, and G are independently CH_2, O, S, SO, SO_2, NH or NR_3 wherein at least 2 of E, F, and G are CH_2;

X is either O or S;

Y is a direct bond to Z, a C_1-C_2 straight or branched chain alkyl, or a C_1-C_2 straight or branched

chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_4)-straight or branched chain alkyl, (C_2-C_4)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_2 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

Z is a direct bond, or a C_1-C_5 straight or branched chain alkyl, or a C_2-C_5 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said

alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_8)-straight or branched chain alkyl, (C_2-C_8)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_2 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

C and D are independently:

hydrogen, Ar, C_1-C_8 straight or branched chain alkyl, or C_2-C_8 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more position(s) with C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl groups are optionally substituted with C_1-C_8 alkyl, C_2-C_8 alkenyl, hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or

alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_3-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

wherein Ar is an aryl or heteroaryl moiety which is substituted or unsubstituted;

W is oxygen or sulfur;

U is either O or N, wherein when U is O, then R_1 is a lone pair of electrons and R_1 is selected from the group consisting of:

Ar as defined above, C_3-C_7 cycloalkyl, C_1-C_6 straight or branched chain alkyl or alkenyl, or C_1-C_6 straight or branched chain alkyl or alkenyl substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_3-C_6 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are

optionally replaced with S, SO, SO_2, O, or NR_2 wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_3-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_6 cycloalkyl;

and when U is N, R_1 and R_2 are selected independently from the group consisting of:

hydrogen, Ar as defined above, C_3-C_6 cycloalkyl, C_1-C_6 straight or branched chain alkyl or alkenyl, or C_1-C_6 straight or branched chain alkyl or alkenyl substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_3-C_6 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2, O, or NR_2 wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_3-C_6)-straight or branched chain alkenyl or alkynyl, and $(C_1-$

C_1 bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_8 cycloalkyl;

or R_1 and R_2 may be taken together to form a heterocyclic ring.

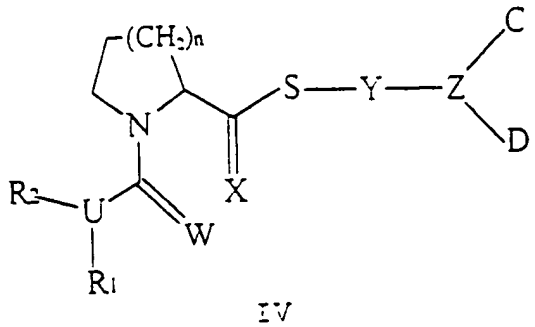
In preferred embodiments, Ar is a cyclic or fused cyclic ring and includes a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted in one to five position(s) with halo, haloalkyl, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_6 alkoxy, C_2-C_6 alkenyloxy, phenoxy, benzyloxy, amino, thiocarbonyl, ester, thioester, cyano, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl; wherein the individual ring sizes are 5-8 members; wherein the heterocyclic ring contains 1-4 heteroatom(s) selected from the group consisting of O, N, or S; wherein aromatic or tertiary alkyl amines are optionally oxidized to a corresponding N-oxide.

Particularly preferred Ar groups include phenyl, benzyl, naphthyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl,

pyrazolyl, and thienyl.

Preferred heterocyclic groups may be selected from the group consisting of pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, thienyl, piperidinyl, and piperazinyl.

A further particularly preferred embodiment of this invention is a compound of formula IV:



IV

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

n is 1, 2 or 3 forming a 5-7 member heterocyclic ring;

X is either O or S;

Y is a direct bond to Z, a C_1-C_3 straight or branched chain alkyl, or a C_2-C_3 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl,

sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_1-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_2 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

Z is a direct bond, or a C_1-C_6 straight or branched chain alkyl, or a C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_1-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl

wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

C and D are independently:

hydrogen, Ar, C_1-C_8 straight or branched chain alkyl, or C_2-C_8 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more position(s) with C_3-C_8 cycloalkyl, C_5-C- cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl groups are optionally substituted with C_1-C_8 alkyl, C_2-C_8 alkenyl, hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_8)-straight or branched chain alkyl, (C_2-C_8)-straight or branched chain alkenyl or alkynyl, and (C_1-C_8) bridging alkyl wherein said

bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

wherein Ar is an aryl or heteroaryl moiety which is substituted or unsubstituted;

W is oxygen or sulfur;

U is either O or N, wherein when U is O, then R_1 is a lone pair of electrons and R_2 is selected from the group consisting of:

Ar as defined above, C_3-C_7 cycloalkyl, C_1-C_6 straight or branched chain alkyl or alkenyl, or C_1-C_6 straight or branched chain alkyl or alkenyl substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2, O, or NR_2 wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_3-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a

heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_9 cycloalkyl;

and when U is N, R_1 and R_2 are selected independently from the group consisting of:

hydrogen, Ar as defined above, C_3-C_9 cycloalkyl, C_1-C_8 straight or branched chain alkyl or alkenyl, or C_1-C_8 straight or branched chain alkyl or alkenyl substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_8 straight or branched chain alkyl, C_1-C_8 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2, O, or NR_2 wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_8)-straight or branched chain alkyl, (C_1-C_8)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_2 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_9 cycloalkyl;

or R_1 and R_2 may be taken together to form a heterocyclic ring.

In preferred embodiments, Ar is a cyclic or fused cyclic ring and includes a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted in one to five position(s) with halo, haloalkyl, hydroxyl, nitro, trifluoromethyl, C_1-C_5 straight or branched chain alkyl, C_2-C_5 straight or branched chain alkenyl, C_1-C_5 alkoxy, C_2-C_5 alkenyloxy, phenoxy, benzyloxy, amino, thiocarbonyl, ester, thioester, cyano, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl; wherein the individual ring sizes are 5-8 members; wherein the heterocyclic ring contains 1-4 heteroatom(s) selected from the group consisting of O, N, or S; wherein aromatic or tertiary alkyl amines are optionally oxidized to a corresponding N-oxide.

Particularly preferred Ar groups include phenyl, benzyl, naphthyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

Preferred heterocyclic groups may be selected from the group consisting of pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, thiophenyl, imidazolyl,

oxazolyl, thiazolyl, pyrazolyl, thienyl, piperidinyl, and piperazinyl.

Particularly preferred compounds of the present invention are selected from the group consisting of:

3-Phenylpropyl (2S)-1-(1-cyclohexylcarbamoyl)-2-pyrrolidinecarbothiate (17);

Phenethyl (2S)-N-(cyclohexylcarbamoyl)-2-pyrrolidinecarbothiate (18);

3-(2,3,5-Trimethylphenyl)propyl 1-(1-adamantylcarbamoyl)-2-pyrrolidinecarbothioate (19);

3-(2,3,5-Trimethylphenyl)propyl 1-(cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (20);

3-(3-Fluorophenyl)propyl (2S)-1-(Cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (21);

3-(2-Fluorophenyl)propyl (2S)-1-(1-adamantylcarbamoyl)-2-pyrrolidinecarbothioate (22);

3-(2-Fluorophenyl)propyl (2S)-1-(cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (23);

3-(4-Methylphenyl)propyl (2S)-1-(cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (24);

3-(4-Methylphenyl)propyl (2S)-1-(1-adamantylcarbamoyl)-2-pyrrolidinecarbothioate (25);

3-(4-Methylphenyl)propyl (2S)-1-(tert-butylcarbamoyl)-2-pyrrolidinecarbothioate (26);

3-(2-Chlorophenyl)propyl (2S)-1-cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (27);

3-(3,5-Dimethoxyphenyl)propyl (2S)-1-{[(1S)-1-(1-naphthyl)ethyl]-carbamoyl}-2-pyrrolidinecarbothioate (28);

3,3-Diphenylpropyl (2S)-1-[(1,1,3,3-tetramethylbutyl)carbamoyl]-2-pyrrolidinecarbothioate (29);

3-Cyclohexylpropyl (2S)-1-[(2,6-diisopropylphenyl)carbamoyl]-2-pyrrolidinecarbothioate (31);

3-Cyclohexylpropyl (2S)-1-(hexylcarbamoyl)-2-pyrrolidinecarbothioate (32);

3,3-Diphenylpropyl (2S)-1-[(2,4-dimethoxyphenyl)carbamoyl]-2-pyrrolidinecarbothioate (33);

3-(3,5-Dimethoxyphenyl)propyl (2S)-1-{[(1S,2R)-2-phenyl-cyclopropyl]carbamoyl}-2-pyrrolidinecarbothioate (34);

3-Phenylpropyl (2S)-1-[(2,4-Dimethoxyphenyl)carbamoyl]-2-pyrrolidinecarbothioate (35);

3-Phenylpropyl (2S)-1-(1-adamantylcarbamoyl)-2-pyrrolidinecarbothioate (36);

3-Phenylpropyl (2S)-1-(1-cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (37);

3-Phenylpropyl (2S)-1-[1-adamantylamino)(thioxo)-methyl]-2-pyrrolidinecarbothioate (38);

3-(3,4,5-Trimethoxyphenyl)propyl (2S)-1-(hexylcarbamoyl)-2-pyrrolidinecarbothioate (39);

3-(3,4,5-Trimethoxyphenyl)propyl (2S)-1-(benzylcarbamoyl)-2-pyrrolidinecarbothioate (40);

3-Phenylpropyl (2S)-1-(dimethylcarbamoyl)-2-pyrrolidinecarbothioate (41);

3-Phenylpropyl (2S)-1-(1-pyrrolidinylcarbamoyl)-2-pyrrolidinecarbothioate (42);

3-Phenylpropyl (2S)-1-(morphilinocarbamoyl)-2-pyrrolidinecarbothioate (43);

3-Phenylpropyl (2S)-1-(diisopropylcarbamoyl)-2-pyrrolidinecarbothioate (44);

3-Phenylpropyl (2S)-1-[methyl(phenyl)carbamoyl]-2-pyrrolidinecarbothioate (45); and

3-Phenylpropyl (2S)-1-(diphenylcarbamoyl)-2-pyrrolidinecarbothioate.

The present invention also relates to a pharmaceutical composition comprising a neurotrophically effective amount of the compound of formula I, II, III or IV, and a pharmaceutically acceptable carrier.

The present invention further relates to a method of effecting a neuronal activity in an animal, comprising:

administering to the animal a neurotrophically

effective amount of the compound of formula I, II, III or IV.

The present invention further relates to the use of any of the compounds of Formula I, II, III, IV or in Table I below in the preparation of a medicament for the treatment of a disease such as peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

The present invention also contemplates processes for manufacturing the novel compounds, particularly the processes delineated below in Schemes 1 and 2.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

"Alkyl" means a branched or unbranched saturated hydrocarbon chain comprising a designated number of carbon atoms. For example, C_1-C_6 straight or branched alkyl hydrocarbon chain contains 1 to 6 carbon atoms, and includes but is not limited to substituents such as methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, tert-butyl, n-pentyl, n-hexyl, and the like, unless otherwise indicated.

"Alkenyl" means a branched or unbranched

unsaturated hydrocarbon chain comprising a designated number of carbon atoms. For example, C_2-C_6 straight or branched alkenyl hydrocarbon chain contains 2 to 6 carbon atoms having at least one double bond, and includes but is not limited to substituents such as ethenyl, propenyl, iso-propenyl, butenyl, iso-butenyl, tert-butenyl, n-pentenyl, n-hexenyl, and the like, unless otherwise indicated.

"Alkoxy" means the group -OR wherein R is alkyl as herein defined. Preferably, R is a branched or unbranched saturated hydrocarbon chain containing 1 to 6 carbon atoms.

"Ar" means an aryl or heteroaryl moiety which is substituted or unsubstituted, especially a cyclic or fused cyclic ring and includes a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted in one to five position(s) with halo, haloalkyl, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_6 alkoxy, C_2-C_6 alkenyloxy, phenoxy, benzyloxy, amino, thiocarbonyl, ester, thioester, cyano, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, and sulfonyl; wherein the individual ring sizes are 3-8 members; wherein the heterocyclic ring contains 1-4 heteroatom(s) selected from the group consisting of O,

N, or S; wherein aromatic or tertiary alkyl amines are optionally oxidized to a corresponding N-oxide. Particularly preferred aryl or heteroaryl moieties include but are not limited to phenyl, benzyl, naphthyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, furyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and thienyl.

"Halo" means at least one fluoro, chloro, bromo, or iodo moiety, unless otherwise indicated.

"Phenyl" includes all possible isomeric phenyl radicals, optionally monosubstituted or multi-substituted with substituents selected from the group consisting of amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_8 straight or branched chain alkyl, C_2-C_8 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, NR_2 wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_8)-straight or branched chain alkyl, (C_2-C_8)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_2 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is

optionally fused to an Ar group.

The term "pharmaceutically acceptable salt, ester, or solvate" refers to salts, esters, or solvates of the subject compounds which possess the desired pharmacological activity and which are neither biologically nor otherwise undesirable. The salt, ester, or solvates can be formed with inorganic acids such as acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, gluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, naphthylate, 2-naphthalenesulfonate, nicotinate, oxalate, sulfate, thiocyanate, tosylate and undecanoate. Base salt, ester, or solvates include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salt with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quarternized with such agents as lower alkyl halides, such as methyl,

ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

The compounds of this invention may possess at least one asymmetric center and thus can be produced as mixtures of stereoisomers or as individual enantiomers or diastereomers. The individual stereoisomers may be obtained by using an optically active starting material, by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis, or by resolution of the compound of formula (I). It is understood that the individual stereoisomers as well as mixtures (racemic and non-racemic) of stereoisomers are encompassed by the scope of the present invention. The S-stereoisomer at atom 1 of formula I is most preferred due to its greater activity.

"Isomers" are different compounds that have the same molecular formula and includes cyclic isomers such as (iso)indole and other isomeric forms of cyclic moieties.

"Stereoisomers" are isomers that differ only in

the way the atoms are arranged in space.

"Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other.

"Diastereoisomers" are stereoisomers which are not mirror images of each other.

"Racemic mixture" means a mixture containing equal parts of individual enantiomers. "Non-racemic mixture" is a mixture containing unequal parts of individual enantiomers or stereoisomers.

The term "preventing neurodegeneration" as used herein includes the ability to prevent neurodegeneration in patients newly diagnosed as having a neurodegenerative disease, or at risk of developing a new degenerative disease and for preventing further neurodegeneration in patients who are already suffering from or have symptoms of a neurodegenerative disease.

The term "treatment" as used herein covers any treatment of a disease and/or condition in an animal, particularly a human, and includes:

(i) preventing a disease and/or condition from occurring in a subject which may be predisposed to the disease and/or condition but has not yet been diagnosed as having it;

(ii) inhibiting the disease and/or condition, i.e., arresting its development; or

(iii) relieving the disease and/or condition, i.e., causing regression of the disease and/or condition.

The system used in naming the compounds of the present invention is shown below, using a compound of formula IV as an example.

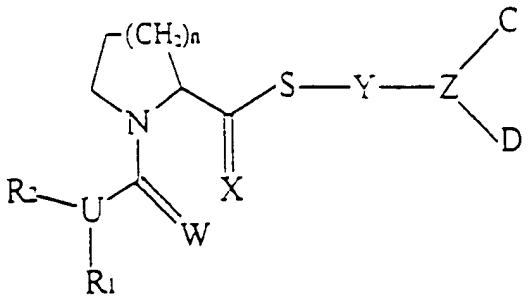
A compound of the present invention, especially Formula IV, wherein n is 1, K is O, Y is $(CH_2)_2$, Z is CH, C is 3-pyridyl, D is H, W is O, U is N, R1 is H and R2 is 2-methylbutyl, is named 3-(3-pyridyl)-1-propylmercaptyl (2s)-1-[(2-methylbutyl) carbamoyl] pyrrolidine-2-carboxylate.

Compounds of the Invention

The neurotrophic low molecular weight, small molecule FKBP inhibitor compounds of this invention have an affinity for FKBP-type immunophilins, such as FKBP12. When the neurotrophic compounds of this invention are bound to an FKBP-type immunophilin, they have been found to inhibit the prolyl-peptidyl *cis-trans* isomerase activity, or rotamase, activity of the binding protein and unexpectedly stimulate neurite growth.

Specific exemplifications of these embodiments are presented in TABLE I.

TABLE I: COMPOUNDS



No	n	W	Y	Z	C	D	R1	R2
1	1	O	$(CH_2)_2$	CH	3-Pyridyl	H	H	2-Methylbutyl
2	1	O	$(CH_2)_2$	CH	3-Pyridyl	H	H	1,1-dimethylpropyl
3	1	O	$(CH_2)_2$	CH	4-Methoxy phenyl	H	H	1,1-dimethylpropyl
4	1	O	CH_2	CH	Phenyl	H	H	1,1-dimethylpropyl
5	1	S	$(CH_2)_2$	CH	4-Methoxy phenyl	H	H	Cyclohexyl
6	1	O	$(CH_2)_2$	CH	3-Pyridyl	H	H	Cyclohexyl
7	1	S	$(CH_2)_2$	CH	3-Pyridyl	H	H	Cyclohexyl
8	1	S	$(CH_2)_2$	CH	3-Pyridyl	H	H	1-Adamantyl
9	1	S	$(CH_2)_2$	CH	3-Pyridyl	H	H	1,1-dimethylpropyl
10	1	O	$(CH_2)_2$	CH	Phenyl	Phenyl	H	1,1-dimethylpropyl
11	2	O	$(CH_2)_2$	CH	Phenyl	H	H	1,1-dimethylpropyl
12	2	O	$(CH_2)_2$	CH	Phenyl	H	H	Phenyl
13	2	O	Direct Bond	CH	2-Phenyl ethyl	2-Phenyl ethyl	H	Phenyl
14	2	O	Direct Bond	CH	2-Phenyl ethyl	2-Phenyl ethyl	H	Cyclohexyl
15	2	S	Direct Bond	CH	2-Phenyl ethyl	2-Phenyl ethyl	H	Cyclohexyl
16	2	O	$(CH_2)_2$	CH	4-Methoxy phenyl	H	H	Cyclohexyl
17	1	O	$(CH_2)_2$	CH	Phenyl	H	H	Cyclohexyl

No	n	W	Y	Z	C	D	R1	R2
18	1	O	CH_2	CH	Phenyl	H	H	Cyclohexyl
19	1	O	$(CH_2)_2$	CH	2,3,5 Trimethylphenyl	H	H	Adamantyl
20	1	O	$(CH_2)_2$	CH	2,3,5 Trimethylphenyl	H	H	Cyclohexyl
21	1	O	$(CH_2)_2$	CH	3-Fluoro phenyl	H	H	Cyclohexyl
22	1	O	$(CH_2)_2$	CH	2-Fluoro phenyl	H	H	Adamantyl
23	1	O	$(CH_2)_2$	CH	2-Fluoro phenyl	H	H	Cyclohexyl
24	1	O	$(CH_2)_2$	CH	4-Methyl phenyl	H	H	Cyclohexyl
25	1	O	$(CH_2)_2$	CH	4-Methyl phenyl	H	H	Adamantyl
26	1	O	$(CH_2)_2$	CH	4-Methyl phenyl	H	H	Tert-butyl
27	1	O	$(CH_2)_2$	CH	2-Chloro phenyl	H	H	Cyclohexyl
28	1	O	$(CH_2)_2$	CH	3,5-Dimeth oxyphenyl	H	H	1-Napthylethyl
29	1	O	$(CH_2)_2$	CH	Phenyl	Phenyl	H	1,1,3,3-Tetramethylbutyl
31	1	O	$(CH_2)_2$	CH	Cyclohexyl	H	H	2,6-Diisopropyl phenyl
32	1	O	$(CH_2)_2$	CH	Cyclohexyl	H	H	Hexyl
33	1	O	$(CH_2)_2$	CH	Phenyl	Phenyl	H	2,4-Dimethoxy phenyl
34	1	O	$(CH_2)_2$	CH	3,5-Dimeth oxyphenyl	H	H	2-Phenylcyclo propyl
35	1	O	$(CH_2)_2$	CH	Phenyl	H	H	2,4-Dimethoxy phenyl
36	1	O	$(CH_2)_2$	CH	Phenyl	H	H	Adamantyl
37	1	O	$(CH_2)_2$	CH	Phenyl	H	H	Cyclohexyl
38	1	O	$(CH_2)_2$	CH	Phenyl	H	H	Adamantyl
39	1	O	$(CH_2)_2$	CH	(3,4,5-Trimethoxy) phenyl	H	H	Hexyl
40	1	O	$(CH_2)_2$	CH	(3,4,5-Trimethoxy) phenyl	H	H	Benzyl

No	n	W	Y	Z	C	D	R1	R2
41	1	O	$(CH_2)_2$	CH	Phenyl	H	CH_3	CH_3
42	1	O	$(CH_2)_2$	CH	Phenyl	H	R_1,R_2= $-CH_2-CH_2-CH_2-CH_2-$ (cyclic)	
43	1	O	$(CH_2)_2$	CH	Phenyl	H	R_1,R_2= $-CH_2-CH_2-O-CH_2-CH_2-$ (cyclic)	
44	1	O	$(CH_2)_2$	CH	Phenyl	H	R_1=R_2=Diisopropyl	
45	1	O	$(CH_2)_2$	CH	Phenyl	H	CH_3	Phenyl
46	1	O	$(CH_2)_2$	CH	Phenyl	H	R_1=R_2=Phenyl	

The compounds of the present invention exist as stereoisomeric forms, either enantiomers or diastereoisomers. Included within the scope of the invention are the enantiomers, the racemic form, and diastereoisomeric mixtures. Enantiomers and diastereoisomers can be separated by methods known to those skilled in the art.

Methods of Using the Compounds of the Invention

The compounds of the present invention have an affinity for the FK506 binding protein, particularly FKBP12, which is present in the neuronal tissue. When the inventive compounds bind to FKBP in neuronal tissue, they exhibit excellent neurotrophic activity. This activity is useful in the stimulation of damaged neurons, the promotion of neuronal regeneration, the prevention of neurodegeneration, and the treatment of several neurological disorders known to be associated with neuronal degeneration and peripheral neuropathies.

For the foregoing reasons, the present invention further relates to a method of effecting a neuronal activity in an animal, comprising:

administering to the animal a neurotrophically effective amount of a compound of formula I, II, III or IV.

In a preferred embodiment, the neuronal activity is selected from the group consisting of stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration and treatment of neurological disorder.

The compounds of the present invention are particularly useful for preventing neurodegeneration in patients suffering from a neurodegenerative disease or who have symptoms of a neurodegenerative disease. The compounds are also useful for preventing neurodegeneration in patients newly diagnosed as having a neurodegenerative disease or at risk for developing a neurodegenerative disease. These compounds are also useful for, but not limited to, preventing neurodegeneration in patients suffering from Parkinson's disease or having symptoms of Parkinson's disease. These treatment methods are exemplified in the MPTP Model and data described herein.

The neurological disorders that may be treated include but are not limited to: trigeminal neuralgia; glossopharyngeal neuralgia; Bell's Palsy; myasthenia gravis; muscular dystrophy; amyotrophic lateral sclerosis; progressive muscular atrophy; progressive bulbar inherited muscular atrophy;

herniated; ruptured or prolapsed invertebrate disk. syndromes; cervical spondylosis; plexus disorders; thoracic outlet destruction syndromes; peripheral neuropathic such as those caused by lead, dapsone, ticks, porphyria, or Guillain-Barré syndrome; Alzheimer's disease; and Parkinson's disease.

The compounds of the present invention are particularly useful for treating a neurological disorder selected from the group consisting of: peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorder relating to neurodegeneration. Examples of neurological disorders relating to neurodegeneration are Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

Pharmaceutical Compositions of the Invention

The present invention also relates to a pharmaceutical composition comprising:

(i) a neurotrophically effective amount of the compound of formula I, II, III or IV, and

(ii) a pharmaceutically acceptable carrier.

The above discussion relating to the utility and administration of the compounds of the present invention also applies to the pharmaceutical

compositions of the present invention.

The term "pharmaceutically acceptable carrier" as used herein refers to any carrier, diluent, excipient, suspending agent, lubricating agent, adjuvant, vehicle, delivery system, emulsifier, disintegrant, absorbant, preservative, surfactant, colorant, flavorant, or sweetener.

For these purposes the compounds of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir in dosage formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intraperitoneally, intrathecally, intraventricularly, intrasternal and intracranial injection or infusion techniques.

For oral administration, the compounds of the present invention may be provided in any suitable dosage form known in the art. For example, the compositions may be incorporated into tablets, powders, granules, beads, chewable lozenges, capsules, liquids, aqueous suspensions or solutions, or similar dosage forms, using conventional equipment and techniques known in the art. Tablet

dosage forms are preferred. Tablets may contain carriers such as lactose and corn starch, and/or lubricating agents such as magnesium stearate. Capsules may contain diluents including lactose and dried corn starch. Aqueous suspensions may contain emulsifying and suspending agents combined with the active ingredient.

When preparing dosage form incorporating the compositions of the invention, the compounds may also be blended with conventional excipients such as binders, including gelatin, pregelatinized starch, and the like; lubricants, such as hydrogenated vegetable oil, stearic acid, and the like; diluents, such as lactose, mannose, and sucrose; disintegrants, such as carboxymethylcellulose and sodium starch glycolate; suspending agents, such as povidone, polyvinyl alcohol, and the like; absorbants, such as silicon dioxide; preservatives, such as methylparaben, propylparaben, and sodium benzoate; surfactants, such as sodium lauryl sulfate, polysorbate 80, and the like; colorants such as F.D.& C. dyes and lakes; flavorants; and sweeteners.

Compositions and methods of the invention also may utilize controlled release technology. Thus, for example, the inventive compounds may be

incorporated into a hydrophobic polymer matrix for controlled release over a period of days. Such controlled release films are well known to the art. Particularly preferred are transdermal delivery systems. Other examples of polymers commonly employed for this purpose that may be used in the present invention include nondegradable ethylene-vinyl acetate copolymer and degradable lactic acid-glycolic acid copolymers which may be used externally or internally. Certain hydrogels such as poly(hydroxyethylmethacrylate or poly(vinylalcohol also may be useful, but for shorter release cycles then the other polymer releases systems, such as those mentioned above.

To be effective therapeutically as central nervous system targets, the compounds of the present invention should readily penetrate the blood-brain barrier when peripherally administered. Compounds which cannot penetrate the blood-brain barrier can be effectively administered by an intraventricular route or other appropriate delivery system suitable for administration to the brain.

The compounds of the present invention may be administered in the form of sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions. These

suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparations may also be sterile injectable solutions or suspensions in non-toxic parenterally-acceptable diluents or solvents, for example, as solutions in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as solvents or suspending mediums. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids such as oleic acid and its glyceride derivatives, including olive oil and castor oil, especially in their polyoxyethylated versions, are useful in the preparation of injectables. These oil solutions or suspensions may also contain long-chain alcohol diluents or dispersants.

The compounds of this invention may also be administered rectally in the form of suppositories. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at room temperature, but liquid at rectal temperature and, therefore, will melt in the rectum

to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The compounds of this invention may also be administered topically, especially when the conditions addressed for treatment involve areas or organs readily accessible by topical application, including neurological disorders of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas.

For topical application to the eye, or ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively for the ophthalmic uses the compounds may be formulated in an ointment such as petrolatum.

For topical application to the skin, the compounds can be formulated in a suitable ointment containing the compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and

water. Alternatively, the compounds can be formulated in a suitable lotion or cream containing the active compound suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Topical application for the lower intestinal tract an be effected in a rectal suppository formulation (see above) or in a suitable enema formulation.

Dosage levels on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 0.1 mg to about 1,000 mg. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the severity of the particular disease being treated and

form of administration.

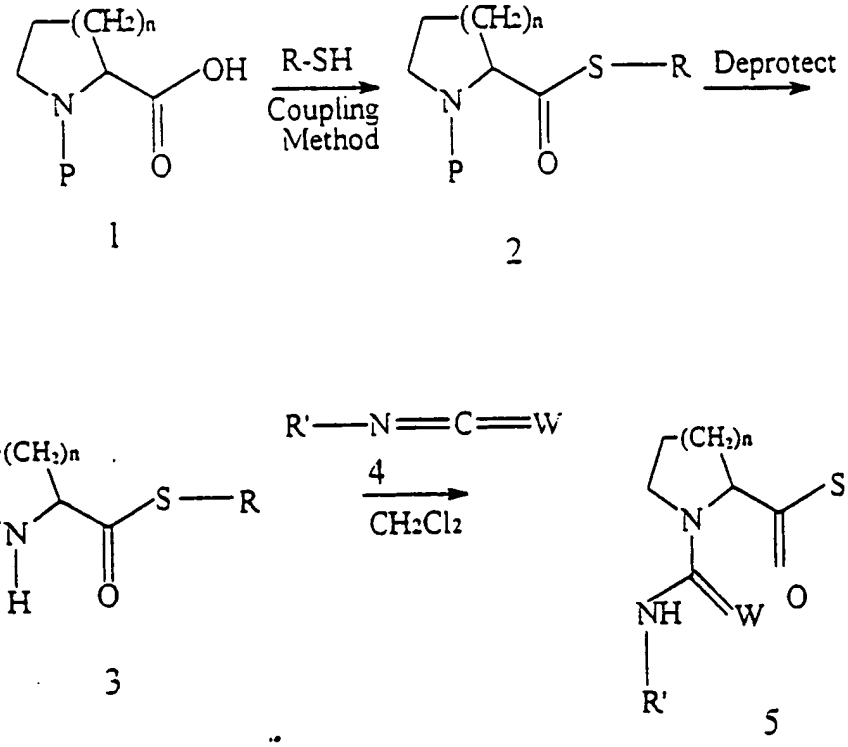
The compounds can be administered with other neurotrophic agents such as neurotrophic growth factor (NGF), glial derived growth factor, brain derived growth factor, ciliary neurotrophic factor, and neurotropin-3. The dosage level of other neurotrophic drugs will depend upon the factors previously stated and the neurotrophic effectiveness of the drug combination.

The present invention relates to the use of any of the compounds seen in Table I in the preparation of a medicament for the treatment of a disease such as peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

The present invention also contemplates processes for manufacturing the novel compounds, particularly the processes delineated in schemes 1 and 2.

Methods of Making the Compounds of the Invention

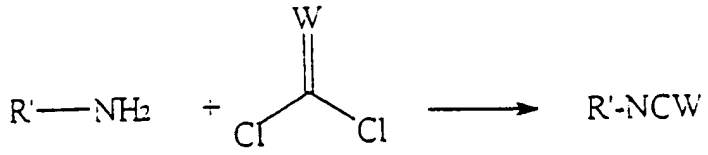
The novel compounds of this invention may be readily prepared by standard techniques of organic chemistry, utilizing the general synthetic pathway depicted below. As described by Scheme 1, cyclic amino acids 1 protected by suitable blocking groups P on the amino acid nitrogen may be reacted with thiols RSH to generate thioesters 2. After removal of the protecting group, the free amine 3 may be reacted with a variety of isocyanates or isothiocyanates to provide the final ureas or thioureas, respectively.



1 2 3 5

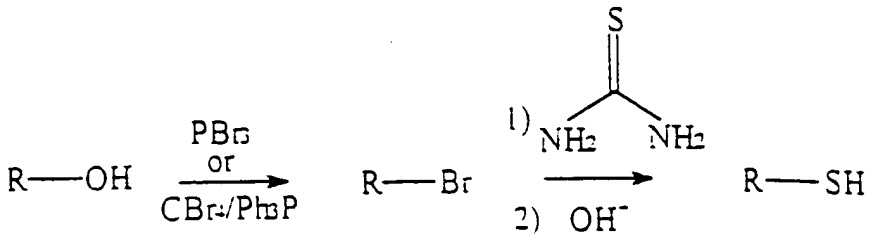
SCHEME 1

Isocyanates (R'NCO) or isothiocyanates (R'NCS) 4 may be conveniently prepared from the corresponding readily available amines by reaction with phosgene or thiophosgene, as depicted in Scheme 2.



SCHEME 2

Thiols R-SH may be conveniently prepared from the corresponding readily available alcohols or halides via a two step replacement of halide by sulfur, as described in Scheme 3. Halides may be reacted with thiourea, and the corresponding alkyl thiouronium salts hydrolyzed to provide thiols RSH. If alcohols are used as the starting materials, they may be first converted to the corresponding halides by standard methods.



SCHEME 3

Examples

The following examples are illustrative of the present invention and are not intended to be limitations thereon. Unless otherwise specified, all percentages are based on 100% by weight of the final compound.

EXAMPLE 1

Synthesis of 3-(3-Pyridyl)-1-propylmercaptyl 2S-1-[(2-methylbutyl)carbamoyl]pyrrolidine-2-carboxylate (1)

3-(3-Pyridyl)-1-propylchloride

To a solution of 3-(3-pyridyl)-1-propanol (10 g; 72.4 mmol) in chloroform (100 mL) was added dropwise a solution of thionyl chloride (12.9 g;

108.6 mmol) in chloroform (50 mL). The resulting mixture was refluxed for 1 hour, then poured into ice-cold 50% aqueous potassium hydroxide (150 mL). The layers were separated, and the organic phase was dried, concentrated, and purified on a silica gel column, eluting with 40% ethylacetate in hexane, to obtain 10 g (65%) of the chloride as a clear oil, ^{1}H NMR (300 MHZ, $CDCl_3$): δ 2.02-2.11 (m, 2H ; 2.77 (m, 2H); 3.51 (m, 2H); 7.20 (m, 1H); 7.49 (m, 1H); 8.45 (m, 2H).

3-(3-Pyridyl)-1-propylmercaptan

A mixture of 3-(3-pyridyl)-1-propylchloride (3 g; 19.4 mmol) and thiourea (1.48 g; 19.4 mmol, in ethanol (10 mL) was refluxed for 24 hours. Aqueous sodium hydroxide, 15 mL of a 0.75 N solution, was added, and the mixture was refluxed for an additional 2 hrs. After cooling to room temperature, the solvent was removed *in vacuo*. Chromatographic purification of the crude thiol on a silica gel column eluting with 50% ethyl acetate in hexane delivered 1.2 g of 3-(3-Pyridyl)-1-propylmercaptan as a clear liquid ^{1}H NMR (300 MHZ, $CDCl_3$): δ 1.34 (m, 1H); 1.90 (m, 2H); 2.52 (m, 2H); 2.71 (m, 2H); 7.81 (m, 1H); 7.47 (m, 1H); 8.42 (m, 2H).

3-(3-Pyridyl)-1-propylmercaptyl N-(tert-butylyoxycarbonyl)pyrrolidine-2-carboxylate

A mixture of N-(tert-butylyoxycarbonyl)-(S)-proline (3.0 g; 13.9 mmol); 3-(3-Pyridyl)-1-propylmercaptan (3.20 g; 20.9 mmol), dicyclohexylcarbodiimide (4.59 g; 22.24 mmol), camphorsulfonic acid (1.08 g; 4.63 mmol), and 4-dimethylaminopyridine (0.60 g; 4.63 mmol) in dry methylene chloride (100 mL) was stirred overnight. The reaction mixture was diluted with methylene chloride (50 mL) and water (100 mL), and the layers were separated. The organic phase was washed with water (3 x 100 mL), dried over magnesium sulfate, and concentrated, and the crude residue was purified on a silica gel column eluting with ethyl acetate to obtain 4.60 g (95%) of the thioester as a thick oil, ^{1}H NMR (300 MHZ, $CDCl_3$): δ 1.45 (s, 9H); 1.70-2.05 (m, 5H); 2.32 (m, 1H); 2.71 (t, 2H); 2.85 (m, 2H); 3.50 (m, 2H); 4.18 (m, 1H); 7.24 (m, 1H); 7.51 (m, 1H); 8.48 (m, 2H).

3-(3-Pyridyl)-1-propylmercaptyl pyrrolidine-2-carboxylate

A solution of 3-(3-Pyridyl)-1-mercaptyl N-(tert-butylyoxycarbonyl)pyrrolidine-2-carboxylate (4.60 g; 13.1 mmol) in methylene chloride (60 mL)

and trifluoroacetic acid (6 mL) was stirred at room temperature for three hours. Saturated potassium carbonate was added until the pH was basic, and the reaction mixture was extracted with methylene chloride (3x). The combined organic extracts were dried and concentrated to yield 2.36 g (75%) of the free amine as a thick oil, ^{1}H NMR (300 MHZ, $CDCl_3$): δ 1.87-2.20 (m, 6H); 2.79 (m, 2H); 3.03-3.15 (m, 4H total); 3.84 (m, 1H); 7.32 (m, 1H); 7.60 (m, 1H); 8.57 (m, 2H).

3-(3-Pyridyl)-1-propylmercaptyl 2S-1-[2-methylbutyl]carbamoylpyrrolidine-2-carboxylate (1)

A solution of 2-methylbutylamine (113 mg; 1.3 mmol) and triethylamine (132 mg; 1.3 mmol) in methylene chloride (5 mL) was added to a solution of triphosgene (128 mg; 0.43 mmol) in methylene chloride (5 mL). The resulting mixture was refluxed for 1 hour and then cooled to room temperature. 3-(3-Pyridyl)-1-propylmercaptyl pyrrolidine-2-carboxylate (300 mg; 1.3 mmol) in 5 mL of methylene chloride was added and the resulting mixture was stirred for 1 hour and then partitioned between water and a 1:1 mixture of ethyl acetate and hexane. The organic phase was dried, concentrated and purified by column chromatography (50% ethyl

acetate/hexane) to obtain 250 mg (55%) of the compound of Example 1 (1, Table I) as an oil, ^{1}H NMR (300 MHZ, $CDCl_3$): d ^{1}H NMR ($CDCl_3$, 300 MHZ): δ 0.89-0.93 (m, 6H); 1.10-1.20 (m, 1H); 1.27 (s, 1H); 1.36-1.60 (m, 2H); 1.72 (s, 2H); 1.97-2.28 (m, 6H); 2.70-2.75 (m, 2H); 2.92-3.54 (m, 6H); 4.45-4.47 (m, 1H); 7.21-7.29 (m, 1H); 7.53-7.56 (dd, 1H); 8.46-8.48 (s, 2H).

Example 2

Synthesis of 3-(3-Pyridyl)-1-propyl 2S-1-[(1',1'-Dimethylpropyl)carbamoyl]pyrrolidine-2-carboxylate (2)

Reaction of 3-(3-pyridyl)-1-propylmercaptyl pyrrolidine-2-carboxylate with the isocyanate generated from tert-amylamine and triphosgene, as described for Example 1, provided the compound of Example 2 (2, Table 1) in 62% yield, ^{1}H NMR ($CDCl_3$, 300 MHZ): δ 0.83 (t, 3H); 1.27 (s, 6H); 1.64-1.71 (m, 2H); 1.91-2.02 (m, 7H); 2.66-2.71 (t, 2H); 2.85 (m, 2H); 3.29-3.42 (m, 2H); 4.11 (br, 1H); 4.37-4.41 (m, 1H).

Example 3

Synthesis of 3-(3-pyridyl)-1-propylmercaptyl 2S-1-[(cyclohexyl)thiocarbamoyl]-pyrrolidine-2-carboxylate

(7)

A mixture of cyclohexylisothiocyanate (120 mg; 0.9 mmol), 3-(3-pyridyl)-1-propylmercaptyl pyrrolidine-2-carboxylate (200 mg; 0.9 mmol) and triethylamine (90 mg; 0.9 mmol) in 20 mL of methylene chloride was the resulting mixture was stirred for 1 hour and then partitioned between water and a 1:1 mixture of ethyl acetate and hexane. The organic phase was dried, concentrated and purified by column chromatography (50% ethyl acetate/hexane) to obtain 160 mg (47%) of the compound of Example 3 (7, Table I), ^{1}H NMR ($CDCl_3$, 300 MHZ): δ 1.16-1.40 (m, 6H); 1.50-1.71 (m, 4H); 1.95-2.08 (m, 7H); 2.70-2.75 (t, 2H); 3.03 (m, 2H); 3.40-3.60 (m, 2H); 4.95-4.98 (d, 1H); 5.26-5.29 (d, 1H); 7.17-7.23 (m, 1H).

EXAMPLE 4

Synthesis of 3-Phenylpropyl (2S)-1-(1-cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate(17)

The compound was prepared in accordance with the procedures used in the above examples and yielded an optically pure compound as a stick white solid, with a chemical formula of $C_{21}H_{33}N_2O_2S$, a molecular weight of 375.56, ^1H NMR ($CDCl_3$, 300 MHZ): δ 1.10-1.19 (m,4H); 1.30-1.38 (m,3H); 1.61-1.71 (m,2H); 1.84-2.03 (m,6H); 2.68 (t,2H,J=7.75); 2.87 (t,2H,J=7.57); 3.33-3.39 (m,1H); 3.46-3.50 (m,1H); 3.63-3.67 (m,1H); 4.18 (d,2H,J=7.85); 4.55 (dd,1H,J=2.14,6.05); 7.11-7.29 (m,5H). Thin Layer Chromatography yielded a result of R_f = 0.43 (50% ETOAc/Hexane).

EXAMPLE 5

Synthesis of Phenethyl (2S)-N-(cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (13)

The compound was prepared in accordance with the procedures used for the above examples and yielded an optically pure compound as a clear oil with a molecular formula of $C_{21}H_{32}N_2O_2S$, molecular weight of 360.63, ^1H NMR ($CDCl_3$, 300 MHZ): δ 1.06-1.38 (m,7H); 1.61-1.72 (m,2H); 1.93-2.13 (m,4H); 2.84 (t,2H,J=7.57); 3.10 (t,2H,J=7.0); 3.33-3.35 (m,1H); 3.44-3.45 (m,1H); 3.64-3.67 (m,1H); 4.17 (bd,1H,J=7.94); 4.55 (bd,1H,J=8.37); 7.20-7.31 (m,5H). Thin Layer Chrmoatography yielded a result

of R_f = 0.18 (50% Hexane:EtOAc).

EXAMPLE 6

Synthesis of 3-(2,3,5-Trimethylphenyl)propyl 1-(1-adamantylcarbamoyl)-2-pyrrolidinecarbothioate (19)

The compound was prepared in accordance with the above examples and yielded an optically pure compound as a colorless oil with a molecular formula of $C_{33}H_{48}N_2O_2S$, molecular weight of 468.66, ^1H NMR ($CDCl_3$, 300 MHZ): δ 1.50 (s,3H); 1.67 (bs,5H); 1.82-1.90 (m,2H); 2.01 (s,6H); 2.15-2.20 (m,4H); 2.10 (s,3H); 2.15 (s,3H); 2.19 (s,3H); 2.63 (t,2H,J=6.66); 3.30 (m,1H); 3.42 (m,1H); 4.15 (s,1H); 4.52 (m,1H); 7.01 (d,2H,J=10.48). Thin Layer Chromatography yielded a result of R_f = 0.82 (80% EtOAc/hexane).

EXAMPLE 7

Synthesis of 3-(2,3,5-Trimethylphenyl)propyl 1-(cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (20)

The compound was prepared in accordance with the procedures used in the above examples and yielded an optically pure compound as a colorless oil with a molecular formula of $C_{24}H_{36}N_2O_2S$-0.75 H_2O, a molecular weight of 430.13, ^1H NMR ($CDCl_3$, 300 MHZ): δ 1.06-1.19 (m,3H); 1.22-1.43 (m,2H); 1.53-1.55

(m,1H); 1.71-1.74 (m,2H); 1.78-1.80 (m,2H); 1.81-1.85 (m,3H); 1.96-2.03 (m,2H); 2.10 (s,3H); 2.15 (s,3H) 2.20 (s,3H); 2.63 (t,2H,J=7.98); 2.90 (t,2H); 3.38 (q,1H); 3.40-3.43 (m,1H); 3.61-3.69 (m,1H); 4.19 (d,1H,J=8.22); 4.56 (d,1H); 6.95 (d,2H,J=12.05). Thin Layer Chromatography yielded a result of R_f = 0.47 (80% EtOAc/hexane).

EXAMPLE 8

Synthesis of 3-(3-Fluorophenyl)propyl (2S)-1-(Cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (21)

The compound was prepared in accordance with the procedures used in the above examples an yielded an optically pure compound as a white solid with a molecular formula of $C_{21}H_{29}N_2OSF$, a molecular weight of 392.56, ^1H NMR ($CDCl_3$, 300 MHZ): δ 1.07-1.43 (m,6H); 1.63-1.73 (m,2H); 1.87-2.09 (cm,7H); 2.67 (t,2H,J=7.46); 2.85 (t,2H,J=7.46); 3.35-3.37 (m,1H); 3.46-3.48 (m,1H); 3.65-3.67 (m,1H); 4.19 (d,1H,J=7.84); 4.55 (d,1H,J=7.90); 6.84-6.95 (m,3H); 7.21-7.24 (m,1H). Thin Layer Chromatography yielded a result of R_f = 0.19 (20% EtOAc/hexane).

EXAMPLE 9

Synthesis of 3-(2-Fluorophenyl)propyl (2S)-1-(1-adamantylcarbamoyl)-2-pyrrolidinecarbothioate (22)

The compound was prepared in accordance with the procedures used in the above examples and yielded an optically pure compound as a colorless oil with a molecular formula of $C_{23}H_{33}N_2O_2SF$, a molecular weight of 444.64, ^1H NMR ($CDCl_3$, 300 MHZ): δ 1.66 (bs,5H); 1.99 (s,2H); 2.04 (bs,6H); 2.06-2.19 (bs,6H); 2.25 (m,1H); 2.69 (t,2H); 2.86 (t,2H); 3.42 (m,1H); 3.57 (m,1H); 4.25 (m,2H); 4.67 (m,1H); 7.05 (m,2H); 7.18 (m,2H). Thin Layer Chromatography yielded a result of R_f = 0.70 (EtOAc).

EXAMPLE 10

Synthesis of 3-(2-Fluorophenyl)propyl (2S)-1-(cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (23)

The compound was prepared in accordance with the procedures used in the above examples and yielded an optically pure compound as a white solid with a molecular formula of $C_{21}H_{29}N_2O_2SF$, a molecular weight of 392.56, ^1H NMR ($CDCl_3$, 300 MHZ): δ 1.23-1.32 (m,3H); 1.41-1.49 (m,3H); 1.74-1.82 (m,2H); 1.93-2.09 (cm,6H); 2.15-2.23 (m,1H); 2.73 (t,2H); 2.94 (t,2H); 3.42-3.51 (m,1H); 3.54-3.61 (m,1H); 3.61-3.74 (m,1H); 4.24 (d,1H); 4.56 (d,1H); 6.91-7.03 (m,2H); 7.15-7.24 (m,2H). Thin Layer Chromatography yielded a result of R_f = 0.65.

EXAMPLE 11

Synthesis of 3-(4-Methylphenyl)propyl (2S)-1-(cyclohexylcarbamoyl)-2-pyrrolidinecarbothicate (24)

The Compound was prepared in accordance with the procedures used in the above examples and yielded an optically pure compound as a white solid with a molecular formula of $C_{22}H_{32}N_2O_2S$-0.25 EtOAc, a molecular weight of 410.60, ^1H NMR ($CDCl_3$, 300 MHZ): δ 1.01-1.21 (m,3H); 1.30-1.44 (m,2H); 1.61-1.69 (m,2H); 1.75-2.13 (cm,8H); 2.30 (s,3H); 2.63 (t,2H); 2.84 (t,2H); 3.61 (q,1H); 3.65-3.69 (m,1H); 3.72-3.76 (m,1H); 4.21 (d,1H); 4.59 (d,1H); 7.05-7.25 (m,4H). Thin Layer Chromatography yielded a result of R_f = 0.84 (80% EtOAc/hexane).

EXAMPLE 12

Synthesis of 3-(4-Methylphenyl)propyl (2S)-1-(1-adamantylcarbamoyl)-2-pyrrolidinecarbothicate (25)

The compound was prepared in accordance with the procedures used in the above examples and yielded an optically pure compound as a colorless oil with a molecular formula of $C_{25}H_{37}N_2O_2S$-0.10 EtOAc, a molecular weight of 450.46, ^1H NMR ($CDCl_3$, 300 MHZ): δ 1.54 (s,5H); 1.66 (bs,6H); 1.85 (q,1H); 2.03 (s,8H); 2.09 (s,4H); 2.63 (t,2H); 2.86 (t,2H); 3.33 (q,1H); 3.35 (m,1H); 4.08 (s,1H); 4.52 (d,1H);

7.03-7.14 (m,4H). Thin Layer Chromatography yielded a result of R_f = 0.68 (80% EtOAc/hexane).

EXAMPLE 13

Synthesis of 3-(4-Methylphenyl)propyl (2S)-1-(tert-butylcarbamoyl)-2-pyrrolidinecarbothioate (26)

The compound was prepared in accordance with the procedures used in the above examples and yielded an optically pure compound as a colorless oil with a molecular formula of $C_{20}H_{30}N_2O_2S$-0.3 H_2O, a molecular weight of 367.94, ^1H NMR ($CDCl_3$, 300 MHZ): δ 1.45 (s,9H); 1.82-1.91 (m,2H); 1.95-2.18 (m,4H); 2.31 (s,3H); 2.76 (t,2H); 2.89 (t,2H); 3.41-3.43 (m,1H); 3.46-3.49 (m,1H); 4.24 (bs,1H); 4.61 (d,1H); 7.09-7.12 (m,4H). Thin Layer Chromatography yielded a result of R_f = 0.50 (50% EtOAc/hexane).

EXAMPLE 14

Synthesis of 3-(2-Chlorophenyl)propyl (2S)-1-cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (27)

The Compound was prepared in accordance with the procedures used in the above examples and yielded an optically pure compound as a light foam with a molecular formula of $C_{21}H_{29}N_2O_2SCl$, a molecular weight of 408.99, ^1H NMR ($CDCl_3$, 400 MHZ): δ 1.05-1.42 (m,7H); 1.61-1.78 (m,3H); 1.83-2.17 (m,5H);

2.87 (t,2H); 3.05 (q,2H); 3.42 (q,1H); 3.57 (m,1H); 3.61-3.67 (m,1H); 4.21 (d,1H); 4.64 (d,1H); 7.20-7.31 (m,3H); 7.56-7.59 (m,1H). Thin Layer Chromatography yielded a result of R_f = 0.78 (EtOAc).

EXAMPLE 15

Synthesis of 3-(3,5-Dimethoxyphenyl)propyl (2S)-1-[[(1S)-1-(1-naphthyl)ethyl]-carbamoyl]-2-pyrrolidinecarbothioate (28)

The compound was prepared in accordance with the procedures used in the above examples and yielded an optically pure compound as a colorless oil with a molecular formula of $C_{29}H_{32}N_2O_3S$-0.75 H_2O-0.60 EtOAc, a molecular weight of 573.04, ^1H NMR ($CDCl_3$, 400 MHZ): δ 1.65 (d,3H,J=6.76); 1.83-1.96 (m,2H); 1.99-2.07 (m,3H); 2.60 (t,2H,J=7.51); 2.85 (t,2H,J=7.27); 3.29-3.68 (m,2H); 3.73 (s,6H); 4.56 (d,1H,J=6.10); 4.76 (d,1H,J=7.51); 5.78-5.79 (m,1H); 6.29-6.32 (m,3H); 7.40-7.76 (m,4H); 7.81 (d,1H,J=6.90); 7.83 (d,1H,J=7.33); 8.17 (d,1H,J=7.72). Thin Layer Chromatography yielded a result of R_f = 0.09 (50% EtOAc/hexane).

EXAMPLE 16

Synthesis of 3,3-Diphenylpropyl (2S)-1-[(1,1,3,3-

tetramethylbutyl)carbamoyl]-2-pyrrolidinecarbothioate (29)

The compound was prepared in accordance with the procedures used in the above examples and yielded an optically pure compound as a colorless oil with a molecular formula of $C_{33}H_{46}N_2O_2S$-0.25 EtOAc, molecular weight of 502.74, ^1H NMR ($CDCl_3$, 400 MHZ): δ 0.88 (t,2H,J=6.57); 1.02 (s,9H); 1.41 (s,3H); 1.42 (s,3H); 1.81 (d,1H,J=14.90); 1.65 (d,1H,J=14.90); 2.04-2.07 (m,1H); 2.29 (q,2H,J=7.83); 2.77 (t,2H,J=6.97); 3.29-3.30 (m,1H); 3.40-3.42 (m,1H); 4.00 (t,1H,J=7.83); 4.32 (s,1H); 4.53 (dd,1H,J=1.96,7.92); 7.10-7.27 (m,10H). Thin Layer Chromatography yielded a result of R_f = 0.43 (50% EtOAc/hexane).

EXAMPLE 17

Synthesis of 3-Cyclohexylpropyl (2S)-1-[(2,6-diisopropylphenyl)carbamoyl]-2-pyrrolidinecarbothioate (31)

The compound was prepared in accordance with the procedures used in the above examples and yielded an optically pure compound as a white solid with a molecular formula of $C_{31}H_{50}N_2O_2S$, a molecular weight of 458.58, ^1H NMR ($CDCl_3$, 400 MHZ): δ 0.76-0.91 (m,2H); 1.15-1.43 (m,18H); 1.59-1.61 (m,2H);

1.63-1.82 (m,5H); 2.09-2.36 (m,4H); 2.83 (t,2H); 3.24 (t,2H); 3.51-3.79 (m,2H); 4.67-4.71 (m,1H) 7.15-7.20 (m,2H); 7.26-7.31 (m,1H). Thin Layer Chromatography yielded a result of R_f = 0.72 (50% EtOAc/hexane).

EXAMPLE 18

Synthesis of 3-Cyclohexylpropyl (2S)-1-(hexylcarbamoyl)-2-pyrrolidinecarbothioate (32)

The compound was prepared in accordance with the procedures used in the above examples and yielded an optically pure compound as a colorless oil with a molecular formula of $C_{21}H_{38}N_2O_2S$-0.05 H_2O, a molecular weight of 483.51, ^1H NMR($CDCl_3$, 400 MHZ): δ 0.76-0.91 (m,2H); 1.15-1.43 (m,18H); 1.59-1.61 (m,2H); 1.63-1.82 (m,5H); 2.09-2.36 (m,4H); 2.83 (t,2H); 3.24 (t,2H); 3.51-3.79 (m,2H); 4.67-4.71 (m,1H); 7.15-7.20 (m,2H); 7.26-7.31 (m,1H). Thin Layer Chromatography yielded a result of R_f = 0.35 (50% EtOAc/hexane).

EXAMPLE 19

Synthesis of 3,3-Diphenylpropyl (2S)-1-[(2,4-dimethoxyphenyl)carbamoyl]-2-pyrrolidinecarbothioate (33)

The compound was prepared in accordance with

the procedures used in the above exmaples and yielded an optically pure compound as a white solid with a molecular formula of $C_{29}H_{32}N_2O_4S$, molecular weight of 504.33, ^1H NMR ($CDCl_3$, 400 MHZ): δ 2.05-2.19 (m,4H); 2.30 (q,2H,J=8.36); 2.78 (td,2H,J=2.89,7.10); 3.58 (q,1H,J=7.57 ; 3.66-3.76 (m,1H); 3.77 (2,3H); 3.80 (s,3H); 3.99 (t,1H,J=7.76); 4.65 (dd,1H,J=2.08,8.12 ; 6.43-6.45 (m,2H); 7.14-7.28 (m,10H); 8.05 (d,1H,J=9.80). Thin Layer Chromatography yielded a result of R_f = 0.63 (EtOAc).

EXAMPLE 20

Synthesis of 3-(3,5-Dimethoxyphenyl)propyl (2S)-1-[[(1S,2R)-2-phenyl-cyclopropyl]carbamoyl]-2-pyrrolidinecarbothioate (34)

The compound was prepare in accordance with the procedures used in the above examples and yielded an optically active compound as an oil with a molecular formula of $C_{29}H_{32}N_2O_4S$-0.4 H_2O, a molecular weight of 475.82, ^1H NMR ($CDCl_3$, 300 MHZ): δ 0.86-0.88 (m,1H); 1.12-1.21 (m,2H); 1.82-1.92 (m,2H); 1.94-2.02 (m,2H); 2.05-2.12 (m,2H); 2.60 (t,2H,J=7.86); 2.84 (dt,2H,J=7.04); 3.33-3.35 (m,1H); 3.46-3.48 (m,1H); 3.75 (s,6H); 4.58 (d,1H,J=6.35); 4.97 (bs,1H); 6.23-

6.32 (m,2H); 7.12-7.25 (m,6H). Thin Layer Chromatography yielded a result of R_f = 0.65 (90% EtOAc/hexane).

EXAMPLE 21

Synthesis of 3-Phenylpropyl (2S)-1-[(2,4-Dimethoxyphenyl)carbamoyl]-2-pyrrolidinecarbothioate (35)

The compound was prepared in accordance with the procedures used in the above examples and yielded an optically active compound as an oil with a molecular formula of $C_{23}H_{30}N_2O_3S$, a molecular weight of 428.57, ^1H NMR ($CDCl_3$, 300 MHZ): δ 1.85-1.90 (m,2H); 2.05-2.19 (m,4H); 2.67 (t,2H,J=7.52); 2.87 (t,2H,J=6.61); 3.53-3.68 (m,1H); 3.72-3.75 (m,1H); 3.77 (s,3H); 3.83 (s,3H); 4.68 (dd,1H,J=2.16,8.11); 6.43-6.46 (m,2H); 6.80 (s,1H); 7.14-7.19 (m,3H); 7.24-7.28 (m,1H); 8.06 (d,1H,J=7.81). Thin Layer Chromatography yielded a result of R_f = 0.45 (50% EtOAc/hexane).

EXAMPLE 22

Synthesis of 3-Phenylpropyl (2S)-1-(1-adamantylcarbamoyl)-2-pyrrolidinecarbothioate (36)

The compound was prepared in accordance with the procedures used in the above examples and

yielded an optically pure compound as a colorless oil with a molecular formula of $C_{23}H_{34}N_2O_2S$, a molecular weight of 426.64, ^1H NMR ($CDCl_3$, 300 MHZ): δ 1.59-1.66 (m,6H); 1.83-2.14 (m,14H); 2.68 (t,2H,J=7.57); 2.86 (t,2H,J=7.23); 3.33-3.45 (m,1H); 4.12 (d,2H,J=7.12); 4.53 (dd,1H,J=2.16,8.16); 7.12-7.29 (m,5H). Thin Layer Chromatography yielded a result of R_f = 0.66 (50% EtOAc/hexane).

EXAMPLE 23

Synthesis of 3-Phenylpropyl (2S)-1-(1-cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (37)

The compound was prepared in accordance with the procedures used in the above examples and yielded an optically pure compound as a sticky white solid with a molecular formula of $C_{21}H_{30}N_2O_2S$, a molecular weight of 375.56, ^1H NMR ($CDCl_3$, 300 MHZ): δ 1.10-1.19 (m,4H); 1.30-1.38 (m,3H); 1.61-1.71 (m,2H); 1.84-2.03 (m,6H); 2.65 (t,2H,J=7.75); 2.87 (t,2H,J=7.57); 3.33-3.39 (m,1H); 3.46-3.50 (m,1H); 3.63-3.67 (m,1H); 4.18 (d,2H,J=7.85); 4.55 (dd,1H,J=2.14,6.05); 7.11-7.29 (m,5H). Thin Layer Chromatography yielded a result of R_f = 0.43 (50% EtOAc/hexane).

Ki Test Procedure

Inhibition of the peptidyl-prolyl isomerase (rotamase) activity of the inventive compounds can be evaluated by known methods described in the literature (Harding, et al., Nature, 1989, 341:758-760; Holt et al. J. Am. Chem. Soc., 115:9923-9938). These values are obtained as apparent Ki's and are presented in Table II. The *cis-trans* isomerization of an alanine-proline bond in a model substrate, N-succinyl-Ala-Ala-Pro-Phe-*p*-nitroanilide, is monitored spectrophotometrically in a chymotrypsin-coupled assay, which releases *para*-nitroanilide from the *trans* form of the substrate. The inhibition of this reaction caused by the addition of different concentrations of inhibitor is determined, and the data is analyzed as a change in first-order rate constant as a function of inhibitor concentration to yield the apparent Ki values.

In a plastic cuvette are added 950 mL of ice cold assay buffer (25 mM HEPES, pH 7.8, 100 mM NaCl), 10 mL of FKBP (2.5 mM in 10 mM Tris-Cl pH 7.5, 100 mM NaCl, 1 mM dithiothreitol), 25 mL of chymotrypsin (50 mg/ml in 1 mM HCl) and 10 mL of test compound at various concentrations in dimethyl sulfoxide. The reaction is initiated by the addition of 5 mL of substrate (succinyl-Ala-Phe-Pro-

Phe-para-nitroanilide, 5 mg/mL in 2.35 mM LiCl in trifluoroethanol).

The absorbance at 390 nm versus time is monitored for 90 seconds using a spectrophotometer and the rate constants are determined from the absorbance versus time data files.

The data for these experiments for representative compounds are presented in Table II under the column "Ki".

The neurotrophic effects of the compounds of the present invention can be demonstrated in cellular biological experiments in vitro, as described below.

Chick Dorsal Root Ganglion

Cultures and Neurite Outgrowth

Dorsal root ganglia were dissected from chick embryos of ten day gestation. Whole ganglion explants were cultured on thin layer Matrigel-coated 12 well plates with Liebovitz L15 plus high glucose media supplemented with 2 mM glutamine and 10% fetal calf serum, and also containing 10 µM cytosine ß-D arabinofuranoside (Ara C) at 37°C in an environment containing 5% CO_2. Twenty-four hours later, the DRGs were treated with various immunophilin ligands. Forty-eight hours after drug treatment, the ganglia

were visualized under phase contrast or Hoffman Modulation contrast with a Zeiss Axiovert inverted microscope. Photomicrographs of the explants were made, and neurite outgrowth was quantitated. Neurites longer than the DRG diameter were counted as positive, with total number of neurites quantitated per each experimental condition. Three to four DRGs are cultured per well, and each treatment was performed in duplicate.

The data for these experiments for representative compounds are presented in Table II under the column "ED_{50}".

TABLE II(a)
In Vitro Test Results

Ex. No.	Ki, nM
1	+++
2	++
3	++
4	++
5	++
6	+
7	++
8	+++
9	+++
10	+++
11	++
12	+++
13	+++
14	+++
15	+++
16	++
18	*
19	*
20	*
21	*
22	+
23	*
24	*
25	+
26	*
27	*
28	*
29	*
31	*
32	*

TABLE II(b)
In Vitro Test Results

Ex. No.	ED50, nM
1	++++
2	+++
3	+++
4	++
5	+++
6	++
7	+++
8	++++
9	++++
10	+++
11	+++
12	+++

13	++++
14	+++
15	++++
16	++

Table II(c): Numerical In Vitro Test Results

Ex. No.	Ki, nM
18	5281
19	10,000
20	665
21	795
22	347
23	545
24	605
25	209
26	739
27	1494
28	8094
29	5147
31	10,000
32	3343
33	10,000
34	2757
35	10,000
36	285
37	601
38	659
39	31
40	82
41	722
42	525
43	3735
44	10,000

†. Relative potencies of compounds are ranked according to the following scale: ++++ denotes Ki or ED50 < 1 nM; +++ denotes Ki or ED50 of 1-50 nM; ++ denotes Ki or ED 50 of 51-200 nM; + denotes Ki or ED of 201-500 nM; * denotes Ki or ED50 of > 500nM.

MPTP Model of Parkinson's Disease

The remarkable neurotrophic and neuroregenerative effects of the present inventive compounds can be further demonstrated in an animal model of neurodegenerative disease. MPTP lesioning of dopaminergic neurons in mice is used as an animal model of Parkinson's Disease. Four week old male CD1 white mice are dosed i.p. with 30 mg/kg of MPTP for 5 days. Test compounds (4 mg/kg), or vehicle, are administered s.c. along with the MPTP for 5 days, as well as for an additional 5 days following cessation of MPTP treatment. At 19 days following MPTP treatment, the animals are sacrificed and the striata are dissected and perfusion-fixed. Immunostaining is performed on saggital and coronal brain sections using anti-tyrosine hydroxylase 1 g to quantitate survival and recovery of dopaminergic neurons. In animals treated with MPTP and vehicle, a substantial loss of functional dopaminergic terminals is observed as compared to non-lesioned animals. Lesioned animals receiving test compounds show a significant recovery of TH-stained dopaminergic neurons. Data from this model presents quantitation for the recovery of TH-positive dopaminergic neurons in the striatum of animals receiving the compounds of the present invention.

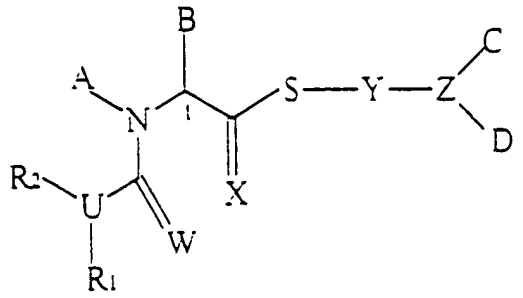
Data from representative control and lesioned animals not receiving the test drugs also presents quantitation of effects in the absence of the compounds of the present invention.

The phrase "preventing neurodegeneration" relates to the remarkable ability of the compounds of the present invention to significantly prevent nerve damage when the compounds are given concurrently with a lesioning agent, such as MPTP. This also provides a reasonable correlation between the scope of the claims and the ability to prevent neurodegeneration in patients newly diagnosed as having a neurodegenerative disease, or at risk of developing a neurodegenerative disease. The compounds also provide methods for preventing further neurodegeneration in patients who are already suffering from or have symptoms of a neurodegenerative disease.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of formula I:



I

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A and B are taken together with the nitrogen and carbon atoms to which they are respectively attached to form a 5-7 membered saturated or unsaturated heterocyclic ring containing any combination of CH_2, O, S, SO, SO_2, NH or NR_3;

X is either O or S;

Y is a direct bond to Z, a C_1-C_4 straight or branched chain alkyl, or a C_2-C_4 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, halcalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH,

NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_3-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_2 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

Z is a direct bond, or a C_1-C_6 straight or branched chain alkyl, or a C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_3-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_2 and ending with one of the carbon atoms of said alkyl or

alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

C and D are independently:

hydrogen, Ar, C_1-C_8 straight or branched chain alkyl, or C_2-C_8 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more position(s) with C_3-C_8 cycloalkyl, C_5-C- cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl groups are optionally substituted with C_1-C_6 alkyl, C_2-C_6 alkenyl, hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_8)-straight or branched chain alkyl, (C_2-C_8)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_2 and ending with one of the carbon atoms of

said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

wherein Ar is an aryl or heteroaryl moiety which is substituted or unsubstituted;

W is oxygen or sulfur;

U is either O or N, wherein when U is O, then R_1 is a lone pair of electrons and R_2 is selected from the group consisting of:

Ar as defined above, C_3-C_7 cycloalkyl, C_1-C_6 straight or branched chain alkyl or alkenyl, or C_1-C_6 straight or branched chain alkyl or alkenyl substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2, O, or NR_3 wherein R_3 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_2-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_3) bridging alkyl wherein said bridging alkyl forms a heterocyclic

ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_7 cycloalkyl;

and when U is N, R_1 and R_2 are selected independently from the group consisting of:

hydrogen, Ar as defined above, C_3-C_7 cycloalkyl, C_1-C_8 straight or branched chain alkyl or alkenyl, or C_1-C_8 straight or branched chain alkyl or alkenyl substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_8 straight or branched chain alkyl, C_2-C_8 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2, O, or NR_2 wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_8)-straight or branched chain alkyl, (C_2-C_8)-straight or branched chain alkenyl or alkynyl, and (C_1-C_3) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is

optionally fused to an Ar group or C_3-C_7 cycloalkyl;

or R_1 and R_2 may be taken together to form a heterocyclic ring.

2. The compound of claim 1, wherein the mono- or bicyclic, carbo- or heterocyclic ring is selected from the group consisting of naphthyl, indolyl, furyl, thiazolyl, thienyl, pyridyl, and phenyl.

3. The compound of claim 1, wherein the compound has an affinity for FKBP-type immunophilins.

4. The compound of claim 3, wherein the FKBP-type immunophilins are FKBP12.

5. The compound of claim 1, wherein the compound inhibits rotamase enzyme activity.

6. The compound of claim 1, wherein the compound is selected from the group consisting of:

3-Phenylpropyl (2S)-1-(1-cyclohexylcarbamoyl)-2-pyrrolidinecarbothiate (17);

Phenethyl (2S)-N-(cyclohexylcarbamoyl)-2-pyrrolidinecarbothiate (18);

3-(2,3,5-Trimethylphenyl)propyl 1-(1-adamantylcarbamoyl)-2-pyrrolidinecarbothioate (19);

3-(2,3,5-Trimethylphenyl)propyl 1-(cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (20);

3-(3-Fluorophenyl)propyl (2S)-1-(Cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (21);

3-(2-Fluorophenyl)propyl (2S)-1-(1-adamantylcarbamoyl)-2-pyrrolidinecarbothioate (22);

3-(2-Fluorophenyl)propyl (2S)-1-(cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (23);

3-(4-Methylphenyl)propyl (2S)-1-(cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (24);

3-(4-Methylphenyl)propyl (2S)-1-(1-adamantylcarbamoyl)-2-pyrrolidinecarbothioate (25);

3-(4-Methylphenyl)propyl (2S)-1-(tert-butylcarbamoyl)-2-pyrrolidinecarbothioate (26);

3-(2-Chlorophenyl)propyl (2S)-1-cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (27);

3-(3,5-Dimethoxyphenyl)propyl (2S)-1-{[(1S)-1-(1-naphthyl)ethyl]-carbamoyl}-2-pyrrolidinecarbothioate (28);

3,3-Diphenylpropyl (2S)-1-[(1,1,3,3-tetramethylbutyl)carbamoyl]-2-pyrrolidinecarbothioate (29);

3-Cyclohexylpropyl (2S)-1-[(2,6-diisopropylphenyl)carbamoyl]-2-pyrrolidinecarbothioate (31);

3-Cyclohexylpropyl (2S)-1-(hexylcarbamoyl)-2-pyrrolidinecarbothioate (32);

3,3-Diphenylpropyl (2S)-1-[(2,4-dimethoxyphenyl)carbamoyl]-2-pyrrolidinecarbothioate (33);

3-(3,5-Dimethoxyphenyl)propyl (2S)-1-[[(1S,2R)-2-phenyl-cyclopropyl]carbamoyl]-2-pyrrolidinecarbothioate (34);

3-Phenylpropyl (2S)-1-[(2,4-Dimethoxyphenyl)carbamoyl]-2-pyrrolidinecarbothioate (35);

3-Phenylpropyl (2S)-1-(1-adamantylcarbamoyl)-2-pyrrolidinecarbothioate (36);

3-Phenylpropyl (2S)-1-(1-cyclohexylcarbamoyl)-2-pyrrolidinecarbothioate (37);

3-Phenylpropyl (2S)-1-[1-adamantylamino)(thioxo)-methyl]-2-pyrrolidinecarbothioate (38);

3-(3,4,5-Trimethoxyphenyl)propyl (2S)-1-(hexylcarbamoyl)-2-pyrrolidinecarbothioate (39);

3-(3,4,5-Trimethoxyphenyl)propyl (2S)-1-(benzylcarbamoyl)-2-pyrrolidinecarbothioate (40);

3-Phenylpropyl (2S)-1-(dimethylcarbamoyl)-2-pyrrolidinecarbothioate (41);

3-Phenylpropyl (2S)-1-(1-pyrrolidinylcarbonyl)-2-pyrrolidinecarbothioate (42);

3-Phenylpropyl (2S)-1-(morphilinocarbonyl)-2-pyrrolidinecarbothioate (43);

3-Phenylpropyl (2S)-1-(diisopropylcarbamoyl)-2-pyrrolidinecarbothioate (44);

3-Phenylpropyl (2S)-1-[methyl(phenyl)carbamoyl]-2-pyrrolidinecarbothioate (45); and

3-Phenylpropyl (2S)-1-(diphenylcarbamoyl)-2-pyrrolidinecarbothioate (46).

7. A pharmaceutical composition comprising a neurotrophically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

8. A method of effecting a neuronal activity in an animal, comprising:

administering to the animal a neurotrophically effective amount of the compound of claim 1.

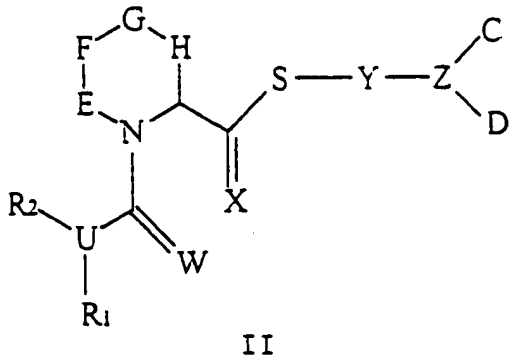
9. The method of claim 8, wherein the neuronal activity is selected from the group consisting of stimulation of damaged neurons, promotion of neuronal regeneration, prevention of

neurodegeneration and treatment of neurological disorder.

10. The method of claim 9, wherein the neurological disorder is selected from the group consisting of peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorder relating to neurodegeneration.

11. The method of claim 10, wherein the neurological disorder relating to neurodegeneration is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

12. A compound of formula II:



II

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

E, F, G and H are independently CH_2, C, S, SO, SO_2, NH or NR_1 wherein at least two of E, F, G, and H are CH_2;

X is either O or S;

Y is a direct bond to Z, a C_1-C_6 straight or branched chain alkyl, or a C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_1, S, SO, or SO_2, wherein R_1 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_2-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

Z is a direct bond, or a C_1-C_6 straight or branched chain alkyl, or a C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of

said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_1-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

C and D are independently:

hydrogen, Ar, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more position(s) with C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl groups are optionally substituted with C_1-C_6 alkyl, C_2-C_6 alkenyl, hydroxy, amino, halo, haloalkyl,

thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_5)-straight or branched chain alkyl, (C_3-C_5)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_2 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

wherein Ar is an aryl or heteraryl moiety which is substituted or unsubstituted;

W is oxygen or sulfur;

U is either O or N, wherein when U is O, then R_1 is a lone pair of electrons and R_2 is selected from the group consisting of:

Ar as defined above, C_3-C_7 cycloalkyl, C_1-C_4 straight or branched chain alkyl or alkenyl, or C_1-C_4 straight or branched chain alkyl or alkenyl

substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2, O, or NR_1 wherein R_1 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_3-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_3) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_7 cycloalkyl;

and when U is N, R_1 and R_2 are selected independently from the group consisting of:

hydrogen, Ar as defined above, C_3-C_9 cycloalkyl, C_1-C_6 straight or branched chain alkyl or alkenyl, or C_1-C_6 straight or branched chain alkyl or alkenyl substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or

branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2, O, or NR_1 wherein R_1 is selected from the group consisting of hydrogen, (C_1-C_8)-straight or branched chain alkyl, (C_3-C_8)-straight or branched chain alkenyl or alkynyl, and (C_1-C_2 bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_8 cycloalkyl;

or R_1 and R_2 may be taken together to form a heterocyclic ring.

13. The compound of claim 12, wherein Ar is selected from the group consisting of naphthyl, indolyl, furyl, thiazolyl, thienyl, pyridyl, and phenyl.

14. The compound of claim 12, wherein the compound has an affinity for FKBP-type immunophilins.

15. The compound of claim 14, wherein the FKBP-type immunophilins are FKBP12.

16. The compound of claim 12, wherein the compound inhibits rotamase enzyme activity.

17. A pharmaceutical composition comprising a neurotrophically effective amount of the compound of claim 12 and a pharmaceutically acceptable carrier.

18. A method of effecting a neuronal activity in an animal, comprising:

administering to the animal a neurotrophically effective amount of the compound of claim 12.

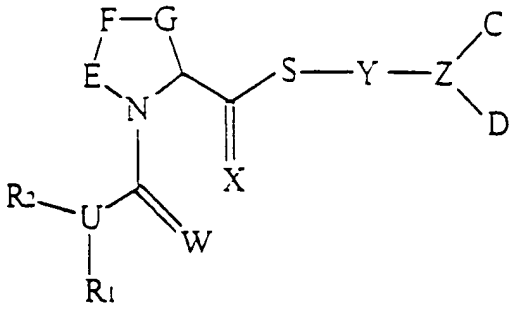
19. The method of claim 18, wherein the neuronal activity is selected from the group consisting of stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration and treatment of neurological disorder.

20. The method of claim 19, wherein the neurological disorder is selected from the group consisting of peripheral neuropathy caused by physical injury or disease state, physical damage to

the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorder relating to neurodegeneration.

21. The method of claim 20, wherein the neurological disorder relating to neurodegeneration is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

22. A compound of formula III:



III

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

E, F, and G are independently CH_2, O, S, SO, SO_2, NH or NR_3 wherein at least 2 of E, F, and G are CH_2;

X is either O or S;

Y is a direct bond to Z, a C_1-C_6 straight or branched chain alkyl, or a C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_2)-straight or branched chain alkyl, (C_3-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl

wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

Z is a direct bond, or a C_1-C_8 straight or branched chain alkyl, or a C_2-C_8 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_4)-straight or branched chain alkyl, (C_2-C_8)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

C and D are independently:

hydrogen, Ar, C_1-C_8 straight or branched chain

alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more position(s) with C_3-C_9 cycloalkyl, C_5-C- cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl groups are optionally substituted with C_1-C_3 alkyl, C_2-C_6 alkenyl, hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_2-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

wherein Ar is an aryl or heteroaryl moiety

which is substituted or unsubstituted;

W is oxygen or sulfur;

U is either O or N, wherein when U is O, then R_1 is a lone pair of electrons and R_2 is selected from the group consisting of:

Ar as defined above, C_3-C_9 cycloalkyl, C_1-C_6 straight or branched chain alkyl or alkenyl, or C_1-C_6 straight or branched chain alkyl or alkenyl substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2, O, or NR_2 wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_3)-straight or branched chain alkyl, (C_3-C_5)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_9 cycloalkyl;

and when U is N, R_1 and R_2 are selected independently from the group consisting of:

hydrogen, Ar as defined above, C_3-C_9 cycloalkyl, C_1-C_6 straight or branched chain alkyl or alkenyl, or C_1-C_6 straight or branched chain alkyl or alkenyl substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2, O, or NR_2 wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_2-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_6) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_9 cycloalkyl;

or R_1 and R_2 may be taken together to form a heterocyclic ring.

23. The compound of claim 22, wherein Ar is selected from the group consisting of naphthyl, indolyl, furyl, thiazolyl, thienyl, pyridyl, and phenyl.

24. The compound of claim 22, wherein the compound has an affinity for FKBP-type immunophilins.

25. The compound of claim 24, wherein the FKBP-type immunophilins are FKBP12.

26. The compound of claim 22, wherein the compound inhibits rotamase enzyme activity.

27. A pharmaceutical composition comprising a neurotrophically effective amount of the compound of claim 22 and a pharmaceutically acceptable carrier.

28. A method of effecting a neuronal activity in an animal, comprising:

administering to the animal a neurotrophically effective amount of the compound of claim 22.

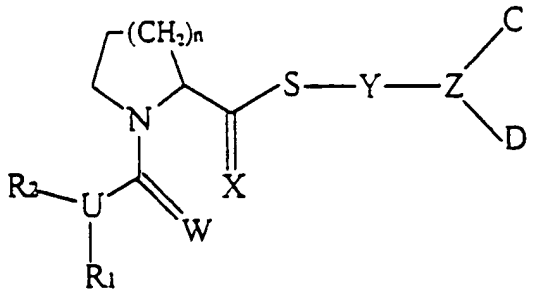
29. The method of claim 28, wherein the neuronal activity is selected from the group consisting of stimulation of damaged neurons, promotion of

neuronal regeneration, prevention of neurodegeneration and treatment of neurological disorder.

30. The method of claim 29, wherein the neurological disorder is selected from the group consisting of peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorder relating to neurodegeneration.

31. The method of claim 30, wherein the neurological disorder relating to neurodegeneration is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

32. A compound of formula IV:



IV

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

n is 1, 2 or 3 forming a 5-7 member heterocyclic ring;

X is either O or S;

Y is a direct bond to Z, a C_1-C_6 straight or branched chain alkyl, or a C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_2-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

Z is a direct bond, or a C_1-C_6 straight or branched chain alkyl, or a C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in

one or more positions with amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_1, S, SO, or SO_2, wherein R_1 is selected from the group consisting of hydrogen, (C_1-C_5)-straight or branched chain alkyl, (C_3-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

C and D are independently:

hydrogen, Ar, C_1-C_6 straight or branched chain alkyl, or C_2-C_6 straight or branched chain alkenyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more position(s) with C_3-C_9 cycloalkyl, C_5-C_7 cycloalkenyl, hydroxyl, carbonyl oxygen, or Ar, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl groups are optionally substituted with C_1-C_6 alkyl, C_2-C_6 alkenyl, hydroxy, amino, halo, haloalkyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy,

cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, wherein any of the carbon atoms of said alkyl or alkenyl are optionally substituted in one or more positions with oxygen to form a carbonyl, or wherein any of the carbon atoms of said alkyl or alkenyl are optionally replaced with O, NH, NR_2, S, SO, or SO_2, wherein R_2 is selected from the group consisting of hydrogen, (C_1-C_6)-straight or branched chain alkyl, (C_3-C_6)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_2 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group;

wherein Ar is an aryl or heteroaryl moiety which is substituted or unsubstituted;

W is oxygen or sulfur;

U is either O or N, wherein when U is O, then R_1 is a lone pair of electrons and R_2 is selected from the group consisting of:

Ar as defined above, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl or alkenyl, or C_1-C_6 straight or branched chain alkyl or alkenyl substituted in one or more positions with Ar, amino,

halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_5 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, carbonyl, thiocarbonyl, ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2, O, or NR_2 wherein R_2 is selected from the group consisting of hydrogen, $(C_1$-$C_6)$-straight or branched chain alkyl, $(C_3$-$C_6)$-straight or branched chain alkenyl or alkynyl, and $(C_1$-$C_4)$ bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_9 cycloalkyl;

and when U is N, R_1 and R_2 are selected independently from the group consisting of:

hydrogen, Ar as defined above, C_3-C_9 cycloalkyl, C_1-C_6 straight or branched chain alkyl or alkenyl, or C_1-C_6 straight or branched chain alkyl or alkenyl substituted in one or more positions with Ar, amino, halo, haloalkyl, hydroxy, trifluoromethyl, C_1-C_5 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, carbonyl, thiocarbonyl,

ester, thioester, alkoxy, alkenoxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, sulfonyl, substituted alkyl or alkenyl wherein any of the carbon atoms of the alkyl or alkenyl are optionally replaced with S, SO, SO_2, O, or NR_1 wherein R_1 is selected from the group consisting of hydrogen, (C_1-C_3)-straight or branched chain alkyl, (C_1-C_3)-straight or branched chain alkenyl or alkynyl, and (C_1-C_4) bridging alkyl wherein said bridging alkyl forms a heterocyclic ring starting with the nitrogen of NR_1 and ending with one of the carbon atoms of said alkyl or alkenyl chain, and wherein said heterocyclic ring is optionally fused to an Ar group or C_3-C_8 cycloalkyl;

or R_1 and R_2 may be taken together to form a heterocyclic ring.

33. The compound of claim 32, wherein Ar is selected from the group consisting of naphthyl, indolyl, furyl, thiazolyl, thienyl, pyridyl, and phenyl.

34. The compound of claim 32, wherein the compound has an affinity for FKBP-type immunophilins.

35. The compound of claim 34, wherein the FKBP-type

immunophilins are FKBP12.

36. The compound of claim 32, wherein the compound inhibits rotamase enzyme activity.

37. A pharmaceutical composition comprising a neurotrophically effective amount of the compound of claim 32 and a pharmaceutically acceptable carrier.

38. A method of effecting a neuronal activity in an animal, comprising:

administering to the animal a neurotrophically effective amount of the compound of claim 32.

39. The method of claim 38, wherein the neuronal activity is selected from the group consisting of stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration and treatment of neurological disorder.

40. The method of claim 39, wherein the neurological disorder is selected from the group consisting of peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord,

stroke associated with brain damage, and neurological disorder relating to neurodegeneration.

41. The method of claim 40, wherein the neurological disorder relating to neurodegeneration is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/24070

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/40; C07D 207/08, 207/12

US CL :514/423, 428; 548/531, 536

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/423, 428; 548/531, 536

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, MEDLINE, BIOSIS
search terms: FKBP?, rotamase?, inhibit?, immunophilin?, thioester?, carbamat?, urea?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,330,993A (ARMISTEAD et al.) 19 July 1994, see entire document.	1-41
Y	US 5,516,797 A (ARMISTEAD et al.) 14 May 1996, see entire document.	1-41
A	SOMERS, et al. Synthesis and Analysis of 506BD, a High-Affinity Ligand for the Innumophilin FKBP. J. Am. Chem. Soc. 09 October 1991, Vol.113, No.21, pages 8045-8056, especially pages 8045-8050.	1-6, 12-16, 22-26, 32-36.

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

18 MARCH 1998

Date of mailing of the international search report

10 APR 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/24070

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-41 in part

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/24070

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

The following table defines the inventions claimed in this application. By selecting a variable from each heading, one can arrive at 256 individual groups:

A, B
pyrrolidinyl
pyridyl
pyrimidyl
oxazole or thiazole

*R_1, R_2
H or non-heterocycle hydrocarbyl
pyridyl or pyrimidyl

Y
direct bond or aliphatic hydrocarbyl
NR_1-alkyl or -alkenyl ring

Z
H, bond, aliphatic hydrocarbyl
NR_1-alkyl or -alkenyl ring

U
oxygen
nitrogen

*Note: proviso that when U is oxygen, R_1 is a lone electron pair.

A sample selection of three (3) individual groups is given below:

Group I, claims 1, 12, 22 and 32, drawn to compounds of formulae I-IV wherein A and B together form pyrrolidine, R_1 is an electron pair, R_2 is hydrogen, C and D are each hydrogen, Y and Z are each a direct bond and U is oxygen. (This is the compound the examiner considers to be the first claimed invention).

Group II, claims 1, 12, 22 and 32, drawn to compounds of formulae I-IV wherein A and B together form pyridine, R_1 is an
electron pair, R_2 is hydrogen, C and D are each hydrogen, Y and Z are each a direct bond and U is oxygen.

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Group CCLVI, claims 1, 12, 22 and 32, drawn to compounds of formulae I-IV wherein A and B together form oxazole or thiazole, R_1 and R_2 together form pyrimidyl, C is an NR_1-alkyl or

-alkenyl ring, D is an NR_1-alkyl or -alkenyl ring, Y is an
NR_1-alkyl or -alkenyl ring, Z is an NR_1-alkyl or -alkenyl ring
and U is nitrogen.

Claims 2-11, 13-21, 23-31 and 32-41 will be examined as commensurate in scope with the group elected.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/24070

The inventions listed as Groups I-CCLVI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: no special technical feature which makes a contribution over the prior art exists within the structures depicted in formulae I-IV in claims 1, 12, 22 and 32. The only structural constants shown are -N-C-C-S- which appear in claim 1 on an otherwise completely variable chain. Nitrogen and sulfur are both known elements. Any contribution over the prior art must, therefore, reside in the possibilities for the various substituents and combinations thereof, which render the compounds different from one another; as such, they are not known as equivalents in the art.